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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/538,223	06/29/2005	Heinz Schneider	09600-00031-US	9409

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EXAMINER	
MCCORMICK, MELENIE LEE	

ART UNIT	PAPER NUMBER
1655	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/538,223	SCHNEIDER, HEINZ	
	Examiner	Art Unit	
	MELENIE MCCORMICK	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-7,9,10,16,18,19,21,25 and 26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-7, 9-10, 16, 18-19, 21, 25 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 14 April 2008 has been entered.

Claims 1-3, 8, 11-15, 17, 20 and 22-24 are cancelled.

Claim 26 has been added.

Claims 3-7, 9-10, 16, 18-19, 21, 25 and 26 are pending and presented for examination on the merits.

Withdrawn Rejections

The previous rejection under 35 U.S.C. 112, first paragraph has been withdrawn in view of the amendments to the claims, which now recite 'reducing the risk of postoperative ischemia-reperfusion injury.

The previous rejection under 35 U.S.C. 103(a) has been withdrawn in view of the claim amendments, which no longer require arginine.

New Rejections

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 16, 18-19, and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Kogirima et al. (JP 2001139481).

Kogirima et al. teach a composition which comprises a green tea extract which contains (+) C (catechin), GC (gallocatechin), EC (epicatechin), EGCg ((-) epigallocatechin gallate), and ECg ((-) epicatechin gallate). Kogirima further teaches that the composition comprises glutamine and theanine (see e.g. abstract). Although Kogirima does not teach that the composition can be used in the manner instantly claimed, the intended use does not offer any structural limitations to the composition. Since Kogirima also teaches that the composition is packaged in container and sterilized and that it is intended to be consumed, nothing would preclude the use of composition taught by Kogirima in the manner instantly claimed (see e.g. abstract).

Therefore, the reference is deemed to anticipate the instant claims above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 3-10, 16, 18-19, and 21-25 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Zhong et al. (2002), Schnieider et al. (US 6,656,608), Sherrat et al. (US 6,423,349), Schnieder et al. (5,902,829), and Yokozowa et al. (2002).

A formulation for gastrointestinal administration to a surgical patient before a surgical procedure to reduce the risk of postoperative ischemia reperfusion injury or to avert such a risk comprising a composition comprising green tea extract and at least one NO donor which is a substrate of NO synthetase, or one precursor of this NO donor, wherein the NO donor and precursor are selected from a group which consists of glutamine and precursors of glutamine in the form of a di or tripeptide containing glutamine or the physiologically acceptable salts or combination thereof is claimed. A method of averting or reducing the risk of postoperative ischemia-reperfusion injury comprising the step of gastrointestinally administering to a surgical patient a composition comprising green tea extract and at least one NO donor which is a substrate of NO synthetase, or one precursor of this NO donor, wherein the NO donor and precursor are selected from a group which consists of glutamine precursors of glutamine in the form of a di or tripeptide containing glutamine or the physiologically acceptable salts or combination thereof is also claimed.

Zhong et al. beneficially teach that Green tea (*Camellia sinensis*) contains high levels of polyphenols including (+) catechin, (-) epicatechin, (+) gallocatechin, (-) epigallocatechin, (-) epicatechin gallate and (-) gallocatechin gallate (see e.g. G957 and Table 1 on page G958). Zhong et al. further teach that green tea extract scavenges free radicals in the liver and after ischemia-reoxygenation (see e.g. abstract). Zhong et al. further teaches that rats were given green tea extract for five days prior to surgery and that hepatic ischemia was induced and then the ischemic liver was repurfused see e.g. pages G957-G958 -Methods).

Schneider et al. '608 beneficially teach that glycine is useful in protecting against damage caused by ischemia reperfusion. Schneider et al. further beneficially teach that a composition comprising glycine is intended to be administered orally (see e.g. col 5 line 66-col 6 line 2). Schneider et al. also further beneficially teach that the composition is intended as a pre-operative treatment (see e.g. col. 6 lines 21-23).

Sherratt et al. beneficially teach that glutamine can be used for promoting recovery in patients undergoing elective surgery and for treating multiple organ system failure (see e.g. col 1, lines 7-10). Sherratt et al. further teach that multiple organ system failure is associated with ischemia reperfusion injury and that oxygen radicals are involved during ischemia followed by reperfusion (see e.g. col 2, lines 38-40). Sherratt also teaches that therapy to prevent the generation of free radicals and to promote the generation of radical scavengers when radicals have been generated are essential to the treatment of multiple organ system failure and that the body's natural antioxidant defenses against free radicals consist primarily of glutathione peroxidase, catalase and

superoxide dismutase (see e.g. col 2, lines 40-47 and lines 59-61). Sherratt also discloses that glutamine has been implicated as sustaining mucosal architecture and function by scavenging free radical and preventing lipid peroxidation. Sheratt also teaches that in addition, glutamine combines with N-acetyl cysteine to form glutathione and, in a reaction catalyzed by the selenium-containing enzyme, glutathione peroxidase, glutathione is transformed to oxidized glutathione. Sherratt et al. further teach that this then combines with hydrogen peroxide and degrades it to water, preventing hydrogen peroxide from reacting with superoxide to produce a hydroxyl radical (see e.g. col 5, lines 22-30). Sherratt et al. further teach a method of promoting recovery from an elective surgical procedure comprising administering to a patient in need thereof, prior to said elective procedure, a composition comprising L-glutamine (see e.g. col 4, lines 8-15). Sherratt et al. further teach that glutamine is a free radical scavenger and that glutamine is administered to patients in order to promote the recovery of elective surgery (see e.g. col 5, lines 22-37 and lines 45-63 and claim 1). Sherratt et al. further teach that the composition is administered to patients prior to elective surgery, particularly for two days prior to the surgery (see e.g. claim 9) and that the administration is oral or via a feeding tube (see e.g. col 10, lines 8-10).

Schneider et al. '829 beneficially teach a composition and a method of administering the composition pre-operatively which reduces the risk of reperfusion injury in patients who undergo elective surgery (see e.g. col 1, lines 21-26). Schneider et al. further teach that L-arginine or a precursor of L-arginine is used for this purpose (see e.g. col 1, lines 27-34). It is further disclosed by Schneider et al. a precursor of L-

arginine which may be used pre-operatively is glutamine (see e.g. col 1, lines 35-36 and claim 4).

Yokozowa et al. beneficially teach that theanine is one of the major components of green tea and that it was able to inhibit lipid peroxidation (see e.g. abstract).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the green tea extract taught by Zhong et al. and the glycine and glutamine taught by Schneider et al. '608 and Sherratt et al. and Schneider '829, respectively, to obtain a composition which would be useful for treating preoperative patients to reduce the risk of ischemia reperfusion. Since it is well known in the art that the majority of damage resulting from ischemia reperfusion is related to oxidative stress, it would have been obvious to the skilled artisan and the skilled artisan would have been motivated and would have had a reasonable expectation of success in combining a well known antioxidant (green tea extract) with glutamine, especially since, as disclosed by Sherratt and Schneider et al. '829, glutamine is useful in protecting against of post operative reperfusion injury. Since it has also been shown that glycine may be useful as a treatment to protect against ischemia reperfusion (as disclosed by Schneider et al. '608), it would have been obvious to include this compound in composition which was to be used for the same purpose. It would have further been obvious to use a green tea extract, such as that taught by Zhong, which contains theanine. A person of ordinary skill in the art would have been motivated to do so based upon the beneficial teaching of Yokazawa et al. that theanine, like polyphenols from

green tea, are a major component in green tea extracts and have antioxidant activity. Therefore, a person of ordinary skill in the art would have recognized the benefit in providing a green tea extract which contains theanine since Sheratt et al. teach that ischemia reperfusion can be reduced by administering radical scavengers (antioxidants) prior to an ischemic event, such as surgery. Please note that the administration times taught by the instantly cited references would render obvious the instantly claimed administration which takes place less than twenty four hours prior to surgery because the references teach administration which *begins* before the surgery. Administration that begins any time prior to surgery and continues until the surgery would be taking place less than twenty four hours prior to surgery, as instantly claimed. The adjustment of particular conventional working conditions (e.g. administering the composition to a patient at a hour before or after surgery) is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan.

Response to Arguments

Although the previous rejection under 35 U.S.C. 103(a) has been withdrawn, arguments pertinent to the current rejection are addressed below.

Applicants argue that the claimed methods are not obvious in view of Inanami et al., Schnieder et al. '608, Sherrat et al. and Schneider et al. '829. This rejection has been withdrawn, and the claims are rendered obvious by the combination of the references in the outstanding rejection, which is discussed above.

Applicants argue that Schneider et al. does not disclose or suggest the use of green tea extract for any purpose, much less to prevent or reduce postoperative complications. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Zhong et al. is relied upon for the teaching that green tea extract scavenges free radicals in the liver and after ischemia-reoxygenation and is useful before surgery.

Applicants argue that they have surprisingly found that the administration of the claimed compound to a surgical patient less than 24 hours before a surgical procedure averts or reduces the risk of postoperative complications. Applicants refer to the Declaration of Dr. Heinz Schneider that shows green tea extract together with glutamine ameliorates ischemia-reperfusion injury, whereas a solution of glutamine in combination with other antioxidants did not provide protection against postoperative complications. This result is acknowledged, however, the particular combination of components would have been obvious to a person of skill in the art at the time of the invention because the art teaches that they are all useful for pre-treatment of surgical patients in order to protect against ischemia reperfusion injury. The only component that would have been obvious to include because of it's antioxidant activity is theanine, however, it is evident that this is the a major component of green tea and would have likely been included in a green tea extract such as that taught by Zhong et al. Nonetheless, the art does teach that reperfusion injury is reduced by the use of antioxidants, as taught by Sherratt. Tus,

a person of ordinary skill in the art would have recognized the potential in reducing reperfusion injury using compounds that are known to do so, including known antioxidants. Therefore, the combination of ingredients is not unexpected. If Applicants are claiming that the ingredients exhibited a synergistic effect, then the particular amounts of the components which achieved this result are critical and would need to be present in the claims in order to demonstrate non-obviousness.

Applicants have discussed the use of glutamine-containing di or tripeptides as sources of glutamine and argue that compositions containing green tea extract and glutamine in the form of a di or tripeptide would also be effective to avert or reduce the risk of post-operative ischemia reperfusion injury. This rationale is accepted, however, the claims as currently written are drawn to a composition and a method using a green tea extract and at least one NO donor which is a substrate of NO synthetase, or one precursor of this NO donor, wherein the NO donor and precursor are selected from a group which consists of glutamine and precursors of glutamine in the form of a di or tripeptide containing glutamine or the physiologically acceptable salts or a combination thereof. Therefore, a di or tri-peptide is not necessarily required of the instant claims. Because glutamine is disclosed by Sherratt et al. and Schneider et al. '829 as being useful in reducing the risk of ischemia reperfusion injury, the use of this compound in a composition to avert or reduce the risk of post-operative ischemia reperfusion injury would have been obvious to one of ordinary skill in the art at the time the claimed invention was made.

Conclusion

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MELENIE MCCORMICK whose telephone number is (571)272-8037. The examiner can normally be reached on M-F 7:30am-4:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on (571) 272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christopher R. Tate/
Primary Examiner, Art Unit 1655

Melenie McCormick
Examiner
Art Unit 1655